January 1956 -
-Dec. '56

Editorial Board

Mark Aisner, M. D., *Chairman*
Charles H. Burnett, M. D.
Maxwell Finland, M. D.
Franz J. Ingelfinger, M. D.
Myron Prinzmetal, M. D.
W. Barry Wood, Jr., M. D.

Disease-a-Month

Glomerulonephritis

DAVID P. EARLE, Jr.

THE YEAR BOOK PUBLISHERS • INC.
CHICAGO

103903

XUM

DM

Disease-a-Month Series

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLE

RECENT and FORTHCOMING ISSUES

Maxwell M. Wintrobe — THE ANEMIAS

A. B. Baker — POLIOMYELITIS

Robert E. Shank — VIRAL HEPATITIS

Arnold S. Relman — RENAL FAILURE

A. Carlton Ernstene — CORONARY ARTERY DISEASE

Max Miller — DIABETES MELLITUS

Thomas P. Almy — CHRONIC AND RECURRENT DIARRHEAS

Lewis Dexter — SURGERY IN HEART DISEASE

Robert H. Ebert — TREATMENT OF TUBERCULOSIS

William Parson and *K. R. Crispell* — OBESITY

Charles Ragan and *Arthur I. Snyder* — RHEUMATOID ARTHRITIS

Julian M. Ruffin and *Donald D. Carter* — PEPTIC ULCER

David P. Earle, Jr. — GLOMERULONEPHRITIS

Sidney Carter and *H. H. Merritt* — CONVULSIVE DISORDERS

COPYRIGHT 1956 BY THE YEAR BOOK PUBLISHERS, INC.
PRINTED IN U.S.A.

XUM

CONTENTS

A. Acute Diffuse Glomerulonephritis 5
B. Outcome of Acute Glomerulonephritis 14
C. Healed Acute Glomerulonephritis 16
D. Subacute Glomerulonephritis 16
E. Chronic Glomerulonephritis 17
F. Hypertension in Glomerulonephritis 23
G. Treatment 24
1. Group A Hemolytic Streptococcus Infections 24
2. Acute Glomerulonephritis 25
3. Exacerbation 29
4. Latent Chronic Glomerulonephritis 29
5. Nephrotic Phase 30
6. Terminal Glomerulonephritis 31

David P. Earle, Jr.

Following graduation from College of Physicians and Surgeons, Columbia University, and a two-year internship, Dr. Earle was a resident on the Columbia Research of the Goldwater Memorial Hospital in New York City. Thereafter he devoted his full time to New York University College of Medicine until he joined the faculty of Northwestern University Medical School in 1954, where he is Professor of Medicine and director of research in the Department of Medicine. Dr. Earle's major research interests and publications have been concerned with the kidneys, from the biological, bacteriological and functional viewpoints.

RECENT DEVELOPMENTS in pathology, bacteriology, immunology, biochemistry and physiology have contributed to advances in our ability to diagnose, interpret and manage the various phases and manifestations of glomerulonephritis. But much is still unknown and unsatisfactory. Indeed, considerable disagreement exists over the definition of glomerulonephritis, and almost every student of the disease eventually proposes his own classification. Some believe that several diseases of different etiologies are included under this diagnosis. Others, however, feel that glomerulonephritis is a single disease which may become manifest in a variety of ways.

Although the diagnosis and interpretation of an individual case of glomerulonephritis sometimes may be quite obvious, especially in the initial acute attack, more commonly the clinician has to weigh judiciously a number of unrelated features, each of which may occur in several different kidney diseases. Proteinuria, impaired renal function, hypertension, edema and many other signs may occur at one time or another during the course of almost any renal disorder. Unfortunately, even the pathologist cannot always help. He can describe quite accurately the structural abnormalities

XUM

present at the time of death. However, in the terminal stages of any chronic renal disease, the organ's architecture may be so distorted that the pathologist is unable to make an unequivocal diagnosis. Although the recently developed technique of renal biopsy may lead to advances in the diagnosis of diffuse kidney disease (1, 2), sometimes the clinician still can make a more accurate diagnosis than the pathologist. The situation leads one to subscribe to the

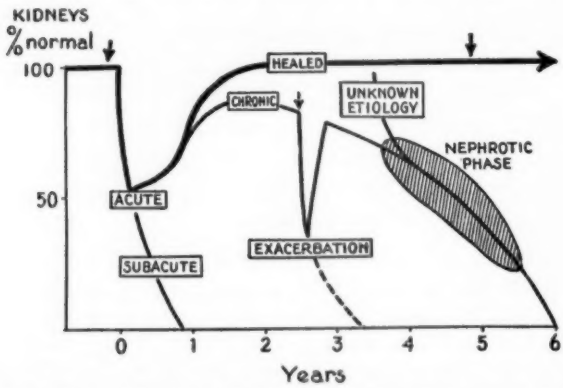

FIG. 1.—Natural history of diffuse glomerulonephritis. Arrows indicate group A hemolytic streptococcus infections. Dashed line below "exacerbation" indicates that a few exacerbations are followed by rapid progression of renal functional impairment, perhaps analogous to the relatively uncommon subacute course subsequent to an initial attack of acute glomerulonephritis.

thoughts expressed by Osler more than 50 years ago when he commented that there were few diseases more conducive to speculation and violent discussions than Bright's disease. The continuation of this state of affairs arises from an interspersing of solid facts in a background of large gaps in our knowledge.

A complete discussion of all aspects of glomerulonephritis will not be attempted here. Excellent descriptions of the pathology and clinical manifestations of the disease are available in a number of textbooks and monographs (3–8). Rather, the author will present

C-749-57

his concepts of the natural history of glomerulonephritis. He hopes that practical points regarding the diagnosis and management of glomerulonephritis will be derived from his considerations of the various phases of the disease. The author's concept of diffuse glomerulonephritis is shown in Figure 1. A number of similarities between this schema and those of other investigators (5, 7) will be apparent. Undoubtedly other students of the disease who will take exception to many of the ideas depicted here, some of which admittedly are based on speculation. Nevertheless, some sort of a conceptual scheme is necessary as a framework for the consideration of a disease as complex as glomerulonephritis.

The abscissa of Figure 1 represents time, while the ordinate represents the "normality" of the kidneys. The term "normality" of the kidneys is used in its broadest sense. The reader should refer to Figure 1 for orientation purposes as the various phases of glomerulonephritis are considered.

A. ACUTE DIFFUSE GLOMERULONEPHRITIS

1. PATHOGENESIS.—Richard Bright, in his classic description of glomerulonephritis (3), recognized its association with upper respiratory infections. Based on careful studies involving frequent throat cultures and antistreptolysin (ASL) titers, Longcope (9) and Lyttle and his co-workers (10) demonstrated that the majority of instances of acute glomerulonephritis follow group A hemolytic streptococcus infections. Indeed, the demonstration of an increase in the ASL titer (and other streptococcal antibodies such as antistreptokinase) is often of considerable diagnostic aid in difficult cases. In view of a rather wide normal range and the fact that a significant increase in ASL titer may occur within the usually accepted normal range, serial measurements are important.

Generally, a latent period of 10 days to four weeks is noted between the infection and the onset of clinical symptoms of acute glomerulonephritis. This observation plus the demonstration that no bacteria are found in the kidneys of patients with acute glomerulonephritis have led a number of investigators to believe that acute diffuse glomerulonephritis is a manifestation of an antigen-

XUM

antibody reaction, somehow set off by a group A hemolytic streptococcus infection.

Recently Rammelkamp and his co-workers (11) have demonstrated that approximately two thirds of the group A hemolytic streptococcus infections preceding acute glomerulonephritis are due to the type 12 organism. Many of the remaining cases are associated with types 4, 18 and 25 group A streptococcus infections. These findings have been confirmed by other investigators (12). Even more recently, an outbreak of acute glomerulonephritis has been described (13) which was due to a specific group A hemolytic streptococcus of a type previously unknown. Apparently, therefore, a limited number of group A hemolytic streptococcus strains may be considered nephritogenic. Such observations suggest the possibility that toxins produced by specific strains of streptococcus rather than an antigen-antibody response may be related to the mechanism of development of acute diffuse glomerulonephritis. This idea has received further support from observations by Rammelkamp and co-workers (14) who studied an outbreak of type 12 hemolytic streptococcal infections in a military training camp. Serial urinalyses in all patients with streptococcus sore throat in this study revealed a high incidence of transient proteinuria and microscopic hematuria a few days after onset of the infection.

However, whether such early occurrence of proteinuria and hematuria represents true glomerulonephritis or some other less specific response to infection is not yet clear. Such findings, for instance, are common in pneumococcus pneumonia. Furthermore, another line of study suggests that antigen-antibody response is an important factor in the development of acute glomerulonephritis. Serum complement is reduced in acute serum sickness and in other antigen-antibody responses both in man and animals. More than 25 years ago several English workers demonstrated a sharp decrease in serum complement in patients with acute glomerulonephritis. By use of improved methods this has been confirmed recently by several other workers (15, 16), who also presented evidence that the decrease in serum complement is not due to its excretion in urine. Further, those instances of experimental glomerulonephritis which most closely resemble the disease seen in man have been pro-

duced through mechanisms almost certainly dependent upon antigen-antibody responses (17, 18).

Thus, it appears fairly safe to conclude that most cases of acute diffuse glomerulonephritis are related in some way to infection with several specific strains of group A hemolytic streptococcus. Although the author believes that available evidence favors an antigen-antibody response, the exact mechanism of production of acute diffuse glomerulonephritis is still unknown. It should be pointed out here that renal disease indistinguishable from acute diffuse glomerulonephritis has been associated with infections due to organisms other than the group A hemolytic streptococcus. These include the pneumococcus (19) and especially Streptococcus viridans and other similar organisms causing subacute bacterial endocarditis (20). This discussion, however, is limited to a consideration of acute diffuse glomerulonephritis of the classic variety (type A nephritis of Longcope (21); type I of Ellis (22)), the majority of cases being related to group A hemolytic streptococcus infections. Reasons will be given later for believing that the insidiously developing nephritis characterized by the nephrotic syndrome (type B of Longcope; type II of Ellis) should be considered separately.

2. A DIGRESSION ON BIOLOGICAL DIFFERENCES BETWEEN ACUTE GLOMERULONEPHRITIS AND RHEUMATIC FEVER.—Rheumatic fever is also quite generally accepted to be related to group A hemolytic streptococcus infections. However, a surprising number of biological differences between the diseases have been described (23). These and several others (12, 15, 24, 25) more recently described are listed in Table 1. Curiously, the incidence of glomerulonephritis in rheumatic fever subjects is no greater than in the general population. For this reason, the development of urinary abnormalities and other evidences of renal disease in rheumatic fever patients should alert the attending physician to the possibility of subacute bacterial endocarditis, which is so commonly associated with renal complications. Such biological considerations suggest that host differences as well as the characteristics of the infecting hemolytic streptococcus are of considerable importance in the mechanisms of development of these diseases.

3. CLINICAL CONSIDERATIONS.—Although acute glomerulone-

phritis is most common in childhood, it can occur at any age. The author has seen initial attacks of acute glomerulonephritis in patients past 60. The disease is twice as common among males as among females. Acute glomerulonephritis can be of any degree of

TABLE 1.—Biological Differences between Glomerulonephritis and Rheumatic Fever

Biological Feature	Glomerulonephritis	Rheumatic Fever
Geographical distribution	Uniform	Most common in northern latitudes
Age	Any age	Rare in infancy
Familial factors	Family contacts	Familial tendency
Sex incidence	Males predominate 2:1	Equal
Second attacks	Rare	Common
Character of preceding infection	"Deep"	"Superficial" pharyngitis
Av. latent period between infection and 1st attack	10 days	18 days
Latent period between infection and 2d attack	Shortened as compared to latent period in 1st attack	Same as latent period in 1st attack
Relation of degree of ASL increase to incidence of attacks	No relation	Incidence of attacks proportional to ASL increase
Time of ASL increase in relation to onset of relapse	After	Before
Serum complement	Decreased	Increased
Type of initiating group A hemolytic streptococcus	4, 12, 18, 25 and untyped (12 predominates)	Any type

severity. Some instances are so mild that the patient has no idea that he is ill at all and, therefore, is not seen by a physician. A number of cases have been picked up during epidemics of hemolytic streptococcus infections in various institutions, on nose and throat services, etc., when daily observations on urine and blood pressure were made. Such mild instances of acute glomerulonephritis, never noticed by the patient, may fail to heal. Many years later the development of uremic symptoms may be the first clue that the patient has been suffering from chronic glomerulonephritis. Routine

urinalyses, however, may have already revealed proteinuria. Although several instances of acute glomerulonephritis without changes in the urine have been described in the literature, and occasionally hypertension and edema may occur several days before urinary abnormalities develop, the author believes that the diagnosis of glomerulonephritis cannot be definite in the absence of proteinuria. Proteinuria is accepted by most authorities as being evidence of glomerular damage. Indeed, it is a more sensitive indicator of glomerular dysfunction than is a decrease in the glomerular filtration rate. Microscopic hematuria is common, and sometimes the urine is grossly bloody or smoky, although the latter are not necessary for the diagnosis. All types of casts may be found in the urine. Red blood cell casts are almost diagnostic. The presence of many leukocytes in the urine may confuse the diagnosis, but they do not occur in clumps as they do in pyelonephritis, nor is significant bacteriuria a feature.

Many but not all patients with acute nephritis also have oliguria, edema, headaches and hypertension. Some impairment of renal function is also common in most of the cases of acute nephritis diagnosed on clinical grounds. In a small percentage of instances the symptoms may be extremely severe, characterized by headaches, convulsions, pulmonary edema and signs of congestion of the circulation. Anorexia, nausea and vomiting are common in the severe cases. Anuria may also occur and uremia may become extreme. Retention of anions (inorganic phosphate, sulfate) contributes to the acidosis common in moderately and severely ill patients whose renal function is significantly reduced. Hyperchloremia is common, even in mildly ill patients. The reason for this is not clear. Electrolyte abnormalities, particularly hyperkalemia, may represent a serious clinical problem in the anuric or severely oliguric patients. Although less than 5 per cent of the patients with acute glomerulonephritis die, the attending physician must constantly be on the alert for the development of excessive increases in blood pressure, which often presage convulsions, and for pulmonary edema. The latter is probably the most common cause of death in acute glomerulonephritis.

4. Renal function.—Measurements of discrete renal functions by the clearance techniques reveal a characteristic pattern of

dysfunction (26, 27) which reflects the anatomical changes of acute glomerulonephritis. The anatomical changes commonly consist of increased cellularity of the tuft (endothelial proliferation, fibrinous thrombi in Bowman's capsular space, infiltration by leukocytes) and fragmentation of the basement membrane. If the basement membrane is severely damaged, hyaline masses may form. The arterioles and the renal tubules are probably relatively little affected at this stage, except in severe cases in which some tubules may be obstructed by casts or damaged by severe anoxia secondary to reduced renal blood flow. Any consideration of renal function in disease should be made in the light of anatomical alterations in the nephrons, especially as revealed by Oliver's classic work (4) on dissections of nephrons in disease. The interested reader is referred particularly to Oliver's delightful essay "When is the Kidney not a Kidney?" (28).

As would be expected from the pathology, the glomerular filtration rate is reduced more than any other renal function. Renal blood flow may also be reduced in severely ill patients but frequently is in the normal range and sometimes may be even greater than normal. This is in contrast to the finding of "bloodless" glomeruli which is so frequently stressed by pathologists who see only fatal cases. Typically, therefore, the filtration fraction (ratio of glomerular filtration rate to renal plasma flow) is reduced in acute glomerular nephritis. This represents a greater barrier to glomerular filtration than to the passage of blood through the glomerular tuft. Function of the proximal renal tubules, as measured by the maximum excretory capacity for p-aminohippuric acid (Tm_{PAH}) or maximum reabsorptive capacity for glucose ($Tm_{glucose}$), also may be reduced. However, in the milder forms of the disease, ratios of renal blood flow to Tm that are greater than normal indicate relative renal hyperemia. Concentrating ability of the kidneys is generally not impaired during the first several days of the initial acute attack. Thereafter, however, the specific gravity becomes fixed at or near 1.010 for weeks or months in most cases.

These characteristic renal functional disturbances persist despite circumstances that are ordinarily associated with quite different patterns of dysfunction. Both congestive heart failure and essential or malignant hypertension are ordinarily associated with greater

reductions of renal plasma flow than of filtration rate, and hence are characterized by an increased filtration fraction. However, when acute nephritis is complicated by hypertension or congestive heart failure, or both, the filtration fraction remains decreased or at least within the normal range (27).

These precise measures of specific renal functions can be of considerable diagnostic assistance. Hypertensive arteriolar nephrosclerosis sometimes may exhibit urinary findings similar to those of acute glomerulonephritis. When the hypertensive patient has, in

TABLE 2.—Typical Renal Function Alterations in Acute Glomerulonephritis, Hypertensive Disease and Congestive Heart Failure

	Acute Glomerulonephritis	Hypertension	Congestive Heart Failure
Glomerular filtration rate (GFR)	Decreased	Normal or slightly decreased	Decreased
Renal plasma flow (RPF)	Increased, normal or decreased	Decreased	Greatly decreased
Filtration fraction (GRF/RPF)	Decreased	Increased	Greatly increased
Max. excretory capacity for PAH (Tm_{PAH})	Decreased	Decreased	Normal or decreased
GFR/Tm_{PAH}	Decreased	Increased	Decreased
RPF/Tm_{PAH}	Increased	Decreased	Decreased

addition, congestive heart failure, the clinical picture easily may be confused with that of acute nephritis. At times, congestive heart failure itself also may be confused with acute nephritis, especially when the heart failure is associated with heavy proteinuria. Further, acute nephritis may sometimes be the cause of congestion of the circulation and occasionally of congestive heart failure (*vide infra*). The clinical picture may be so dominated by the circulatory manifestations that its renal origin is overlooked. Although pyelonephritis is rarely associated with edema, it too at times may be confused on clinical grounds with glomerulonephritis. Typical effects of two of these conditions on several renal functions and their inter-relations are compared to those of acute glomerulo-

nephritis in Table 2. Such differentiations are not always possible, especially when renal failure is advanced. Further diagnostic assistance may be obtained from the ASL titer and serum complement level, which are characteristically altered in acute nephritis (pp. 5 ff.).

Although routine clinical use of the specific measures of discrete renal functions is not yet feasible, some of the simpler measures of renal function are of considerable value, especially if interpreted in light of their relations to the more specific measurements (29). The urea and creatinine clearances, for instance, are more a reflection of glomerular filtration rate than of any other renal functions. The urea clearance, however, is less than the filtration rate by virtue of passive back-diffusion of some of the filtered urea across the tubules. The urea clearance, furthermore, varies directly with the urine flow. Some creatinine is excreted by the renal tubules of man, and hence its clearance is greater than glomerular filtration rate.

Likewise, phenolsulfonthlein (PSP) excretion, as the test is ordinarily performed, is a crude measure of renal plasma flow. This stems from the fact that PSP is removed so rapidly by the renal tubules from the blood flowing through the kidneys that its excretion rate in the normal subject is dependent upon its rate of delivery to the kidneys. However, as renal disease advances and the ability of the renal tubule cells to extract PSP becomes impaired, its excretion rate becomes more a reflection of decreased tubular function than of renal blood flow. At what stage of renal tubule functional impairment PSP excretion becomes more a reflection of tubular function than of renal blood flow is not certain. The dividing line is probably somewhere in the neighborhood of one third to one quarter of normal renal function (as measured by tubular excretory capacity).

5. Edema.—Edema is one of the common manifestations of acute glomerulonephritis. Considerable disagreement exists as to its pathogenesis. Apparently, most investigators (6, 8, 30) believe that edema in acute glomerulonephritis is mostly the result of congestive heart failure. This conclusion usually is based on the belief that acute hypertension can lead to myocardial insufficiency or that myocardial damage can be produced by acute glomerulonephritis. Either one or both of these mechanisms are then assumed

to be the basis for the apparent manifestations of congestive heart failure. Those observers who subscribe to the thought that congestive heart failure is common in acute glomerulonephritis point to the facts that the heart may be enlarged, that pulmonary edema is not uncommon and that in the moderately severe to severely ill patient venous pressure may be increased and the liver may be palpable. However, several potent arguments may be summoned against this thesis. Cardiac output, for instance, is rarely decreased and may, indeed, be increased above normal (31). Although venous pressure frequently may be elevated, circulation time is normal or rapid. Such findings are not compatible with ordinary low cardiac output congestive heart failure. Rather, these manifestations may be the result of congestion of the circulation due to salt and water retention in the presence of a normal heart, somewhat similar to the situation in a patient with acute renal failure due to carbon tetrachloride poisoning who has been given excessive amounts of fluid. Another line of evidence which suggests a mechanism for edema formation other than congestive heart failure is furnished by the recent studies of Farber and Soberman (32). These workers find that more sodium in relation to total body water is retained by patients with congestive heart failure than by patients with edema due to glomerulonephritis.

Other observers believe that generalized capillary damage may account for the edema in most instances of acute nephritis. This belief has been based chiefly on the localization of edema around the face and eyes, on the occurrence of edema and hypertension prior to or even without urinary abnormalities and on the older observations that the edema fluid of acute glomerulonephritis contains relatively large amounts of protein. However, obvious accumulation of edema in the tissues of the face and elsewhere is not surprising in patients with fluid retention who are confined to bed and who do not have local or general elevation of venous pressure. Observations in 1944 (33) on the edema fluid of acute nephritis indicate that it has the low protein content characteristic of transudates rather than the high protein content of fluids characteristic of inflammatory reactions or of generalized capillary damage. Extensive generalized capillary damage should lead to considerable loss of protein and fluid from the vascular system. This should re-

sult in an increase in the hematocrit. The usual observation in acute nephritis, however, is a decrease in hematocrit and a subsequent return to normal following diuresis. These findings could be explained more easily on the basis of congestion of the circulation secondary to fluid retention than they could on the basis of generalized capillary damage.

The author, therefore, feels that considerable emphasis should be placed upon a renal mechanism for fluid and salt retention in acute nephritis. The observed reduction of filtration rate may well play some role in the pathogenesis of nephritic edema. This is especially likely in patients whose filtration rate is rapidly and suddenly reduced. However, patients have been noted to have massive edema even though the glomerular filtration rate was within the normal range (27). Furthermore, the urea clearance in acute glomerulonephritis is not infrequently reduced out of proportion to the filtration rate and out of proportion to the degree of oliguria (27). Since reabsorption of urea by the renal tubules appears to represent passive diffusion, a possible explanation for the low urea/inulin clearance ratio in most instances of acute glomerulonephritis could be renal epithelial cell damage. In any case, data have been accumulated to indicate that diuresis during recovery from an episode of acute nephritis can take place without any increase at all in glomerular filtration rate or renal blood flow (27). At the same time, urea clearance frequently increases, but this increase is not entirely dependent upon the rate of urine flow. Whether such changes are due to damage and restoration thereafter of the renal epithelial cells, are the result of changes in the renal interstitial tissue or are due to other unknown factors, is not certain.

B. OUTCOME OF ACUTE GLOMERULONEPHRITIS

Because of the difficulty or impossibility of diagnosing all mild cases of acute nephritis and because of differences in opinions, definitions and criteria, it is not possible to arrive at a precise estimate of the prognosis of acute glomerulonephritis. Nevertheless, it is the consensus of the majority of competent students of the disease that at least 85 per cent and perhaps even more of patients with acute glomerulonephritis will recover completely. Failure to

distinguish between the exacerbation in chronic glomerulonephritis and the initial acute attack probably accounts for the belief that acute nephritis in adults is quite likely to become chronic.

Excluding the minority who die in the initial acute attack or who go on to the progressive subacute form of the disease, patients will show marked improvement in all signs and symptoms and in renal function. Proteinuria, however, may continue for weeks or months. At present, there are no means to differentiate between those patients whose nephritis eventually will heal and those who will progress into chronic nephritis. Two years may be required for the proteinuria to clear up. Some degree of microscopic hematuria and impaired ability to concentrate the urine may persist for six to 12 months after the disappearance of proteinuria and yet be compatible with healing. Persistent proteinuria one or two years after the initial acute episode, however, generally means that the patient has gone into the latent phase of chronic glomerulonephritis. Serial observation at monthly intervals for proteinuria, therefore, is essential in the follow-up period. Care must be taken to restrict fluids for 12 hours before collecting the urine for analysis, since even a moderate diuresis may obscure minimal but significant proteinuria. Proteinuria generally disappears within three to six months in patients in whom the nephritis heals. Nevertheless, a few patients may have proteinuria for as long as two years and still have the lesion heal. The wise clinician, therefore, will not make the gloomy diagnosis of chronic glomerulonephritis hastily.

The factors concerned with the outcome of a given attack of acute glomerulonephritis are not known. However, no evidence exists that the outcome is necessarily related to the persistence or absence of the offending group A hemolytic streptococcus. For instance, a number of patients have been observed in whom acute nephritis healed completely despite the persistence of group A hemolytic streptococci in throat cultures, or even despite chronic infection due to this organism. Conversely, other patients have been observed to go into the subacute or latent phases of chronic glomerulonephritis with no further evidence whatever of persistence of group A hemolytic streptococcus infection. Nor does the outcome appear to be related to the severity of the initial attack. Many observers have noted that the most severe uremic manifesta-

tions in acute nephritis are compatible with complete healing. Other investigators have commented on the fact that patients with the greatest hematuria are often those with the most benign course and with the most rapid recovery. Conversely, the acute episode may be so mild as to escape the patient's attention and yet fail to heal, leading to uremia later in life. Hence, renal function studies during the early stages of acute nephritis have been of little or no assistance in arriving at an accurate prognosis. They are useful, however, in following the trend of the disease and can help to disclose those patients who are going into the subacute phase.

C. HEALED ACUTE GLOMERULONEPHRITIS

A patient whose nephritis has healed is in a very strategic position. Second attacks of this disease are extremely uncommon. The author has seen only one case. Loeb and her colleagues (34) followed a number of patients with healed acute nephritis through subsequent, proved group A hemolytic streptococcus infections. Although a few of them had mild and transient proteinuria and hematuria, none developed other evidence of second attacks of acute glomerulonephritis. The reason for the infrequency of second attacks of nephritis, in contrast to second attacks of rheumatic fever, is not exactly clear. However, the existence of only a few nephritogenic strains of group A hemolytic streptococci may be the explanation. A fairly solid immunity to subsequent reinfection with a particular strain of streptococcus would further reduce the chances of a second attack of acute glomerulonephritis. Thus, a distinct possibility exists that the infrequency of second attacks of this disease results from the statistical unlikelihood of a given patient becoming infected with a second rare nephritogenic strain of hemolytic streptococcus.

D. SUBACUTE GLOMERULONEPHRITIS

Of the patients who survive the acute attack of glomerulonephritis, less than 2 per cent will develop a rapidly progressive disease and die within three to 12 months. Simply on the basis of duration, these patients are said to have subacute glomerulonephritis. The

histological picture in such patients frequently, but not always, is characterized by many crescents in the glomerular tufts. Unfortunately, crescents also may be found in patients who die after a more prolonged disease that hardly could be classified subacute. Although hypertension, edema and other symptoms in patients with subacute nephritis sometimes clear quite rapidly after the acute episode, renal function undergoes a rapid and progressive impairment. These patients usually die within eight to 12 months. During the course of the disease, elements of the nephrotic syndrome may appear. In others, progressive hypertensive cardiovascular disease with convulsions and congestive heart failure may develop rather suddenly. Again, the reasons why a few patients develop this subacute course are not clear.

E. CHRONIC GLOMERULONEPHRITIS

1. LATENT PHASE.—Since the latent phase may be characterized only by proteinuria, several years may pass before a diagnosis of chronic glomerulonephritis can be made with assurance. Once persistent proteinuria has established the diagnosis of chronic glomerulonephritis, an accurate prognosis is still difficult in view of great variability in the rate of progression of the disease.

Except for the proteinuria, no evidence of renal disease may be detectable in most patients on the basis of simple clinical evaluation. Throughout the early course of chronic glomerulonephritis, hypertension is uncommon and clinical measures of renal function, such as PSP excretion, urea clearance and concentrating ability, may be normal or only slightly reduced. However, precise measurements of renal function may disclose definite evidence of functional impairment (26). The usual pattern of dysfunction seen in this stage is a greater reduction of filtration rate than of blood flow and, therefore, a decreased filtration fraction. Tubular function, as reflected by Tm_{PAH} or $Tm_{glucose}$, also may be reduced in the latent phase of chronic glomerulonephritis. However, these functions are less affected than is filtration rate, as indicated by relatively low filtration rate to Tm ratios.

The latent stage may persist for several years or as long as 30 years. Sooner or later, however, the course is gradually downhill,

with progressive impairment of renal function. Even in the presence of moderately advanced renal failure and nitrogen retention, the patient may feel quite well and be able to carry on his ordinary daily affairs until uremia and some of its complications such as anemia, acidosis and heart failure develop.

2. EXACERBATION.—Seegal and his colleagues (35) have defined arbitrarily the exacerbation in chronic glomerulonephritis as an abrupt and marked increase in the degree of hematuria. They pointed out that slight variations in the urinary excretion of erythrocytes do not necessarily signify an exacerbation. Most instances of exacerbation are associated with the other manifestations ordinarily found in the initial acute attack of glomerulonephritis, such as transient hypertension, edema and decrease in renal functions. Proteinuria and cylindruria also usually increase but cannot always be used as criteria for an exacerbation since the values may already be high.

All patients with chronic glomerulonephritis do not have exacerbations. For instance, in one study (24), 33 exacerbations were observed in 15 of 81 patients studied over periods ranging from four months to eight years. Each exacerbation was preceded by an upper respiratory tract infection, the majority of which were shown to be associated with group A hemolytic streptococci. No information is available as to whether or not exacerbations in chronic glomerulonephritis are associated with infections due to the known nephritogenic strains of the hemolytic streptococcus. Since a single infection with a particular strain probably yields lasting immunity, it is a little difficult to understand how a single patient could undergo three or more exacerbations in chronic glomerulonephritis all due to the same strain of streptococcus. Perhaps in some unknown way a patient with chronic glomerulonephritis can respond to infection due to any strain of group A hemolytic streptococcus with a clinical syndrome similar to acute glomerulonephritis.

The exacerbation is generally associated with a considerable decrease in renal function. It generally soon returns to the level observed before the exacerbation, although this level usually has been somewhat below normal (Fig. 1). In view of such observations, and since all individuals with chronic glomerulonephritis do not have exacerbations, the author agrees with Seegal (35) that exacerba-

tions appear to contribute little if anything to the progression of the disease. Rather, the exacerbations appear to be episodes in the course of chronic glomerulonephritis. In a few instances, however, an exacerbation has appeared to cause a rapid progression in the underlying renal disease, as shown by the dashed line in Figure 1. This may be comparable to the subacute phase following the initial acute attack.

Sometimes, if the patient's history is unknown, it may be difficult to distinguish between the initial acute episode of glomerulonephritis and the exacerbation of chronic nephritis, since they can be quite similar. One useful differential point is the short latent period between the onset of the preceding infection and the onset of the exacerbation. This is only a day or so, in contrast to the usual seven to 28 day latent period between the infection and the initial acute episode of glomerulonephritis. Of course, if the patient's nephritis heals, one can distinguish in retrospect between the two, for chronic glomerulonephritis rarely if ever heals. The author agrees with Seegal and his colleagues in their concept that the exacerbation in chronic glomerulonephritis represents more or less a clinical replica of the initial attack.

The development of the nephrotic phase or a rather abrupt increase in the tempo in renal functional deterioration does not necessarily represent a true exacerbation in chronic glomerulonephritis. These two features rarely if ever can be shown to be associated with hemolytic streptococcus infections, and hence are different from both the initial acute episode and the exacerbation as defined earlier. They are, however, of considerable practical and academic importance and may indeed represent some type of activity in the renal process, even though it is not similar to the initiating episode.

3. NEPHROTIC PHASE.—The nephrotic syndrome may be defined as massive edema, heavy proteinuria, hypoalbuminemia and hypercholesteremia. Bloom and Seegal (36) found evidence of this syndrome in approximately half of 50 patients at one time or another during the course of chronic glomerulonephritis. This syndrome also may occur in other diseases such as syphilis of the kidneys, disseminated lupus erythematosus, renal amyloidosis, Kimmelstiel-Wilson syndrome, renal vein thrombosis, following the administra-

XUM

tion of certain drugs such as Dilantin, and in true lipoid nephrosis. Of diagnostic value is the fact that the nephrotic syndrome rarely if ever is associated with primary hypertensive renal disease, arteriosclerotic renal disease or pyelonephritis.

Although the nephrotic phase ordinarily develops after several years of latent chronic glomerulonephritis, elements of it also can occur in the subacute phase, and in several instances has been observed to develop within a few weeks of the onset of acute glomerulonephritis (37, Case 1). The latter, however, is very uncommon. When the nephrotic phase develops in chronic nephritis, it generally occurs at a time when renal function has not been greatly impaired and when hypertension has not yet developed. The nephrotic syndrome may last for several months or several years. During the course of a nephrotic syndrome, renal function usually undergoes a progressive decrease. Hypertension and uremia may develop toward the end of the nephrotic stage. Apparently, when the decrease in glomerular filtration rate is great enough, the amount of the protein lost in the urine diminishes to negligible amounts. As a consequence of this, the serum albumin level increases and the nephrotic syndrome disappears. If not already present, hypertension and uremia develop at this time or soon thereafter because of the advancing renal failure.

Although almost all workers agree that the nephrotic syndrome can occur during the course of chronic glomerulonephritis which followed acute nephritis due to group A hemolytic streptococcus infections, several students of the disease believe that the nephrotic phase of chronic glomerulonephritis frequently represents an entirely different disease, or at least a disease of different etiology. This belief is based in part on the infrequency of bacteriological or immunological evidence of group A hemolytic streptococcus infections preceding the development of the nephrotic syndrome. Indeed, evidence of any type of infection may be lacking. Many patients do not exhibit the hematuria and hypertension so common in classic acute glomerulonephritis. This situation has been designated type B nephritis by Longcope (21) and type II nephritis by Ellis (22), in contrast to type A and type I, which represent to these authors ordinary acute hemorrhagic glomerulonephritis.

The common denominator for all instances of the nephrotic

syndrome is the loss in the urine of large amounts of protein, mostly albumin but also other protein fractions, including gamma globulin. Loss of gamma globulin, which contains antibodies, probably accounts for the increased susceptibility of the nephrotic patient to bacterial infections. Most investigators agree that loss of serum proteins into the urine is the result of glomerular damage. The author believes, therefore, that the nephrotic syndrome represents more or less an anatomical accident that can occur in a number of renal diseases and that no particular need exists for interpreting the development of the nephrotic syndrome in chronic glomerulonephritis as "renal activity," at least of the type of activity present in the initial acute attack or exacerbation. Nevertheless, other students of the disease believe that the development of the nephrotic syndrome represents a manifestation of an antigen-antibody reaction (38). This is based on experimental work in animals and on the observation that serum complement may decrease in the nephrotic syndrome, especially in children (16). Decreased serum complement in the nephrotic phase, however, may be an artefact. Although some instances of the nephrotic phase in chronic glomerulonephritis may result from an antigen-antibody reaction, the author believes that many instances simply represent a stage in the progressive glomerular damage characteristic of glomerulonephritis.

4. Terminal glomerulonephritis.—As chronic glomerulonephritis progresses to the terminal stage, the patient becomes listless, weak and pale. Anemia usually does not become marked until nitrogen retention is well established and for the most part appears to be the result of suppression of the bone marrow. A hemolytic process, however, may also play some role.

At this stage, tubular function may undergo a relatively more rapid impairment than the glomerular filtration rate. This is indicated by increasing loss of PSP excretory function and of concentrating ability, and by increasing filtration rate to Tm ratios. Thus, as the disease progresses the symptoms of renal insufficiency may become more manifest because of a general distortion of the normal relationships of the component parts of some or all of the nephrons, as a result of loss of nephrons, or because of a combination of both.

The absolute loss of renal functional tissue is responsible for the

XUM

reduced ability of the kidneys to form ammonia and hence to combat acidosis and also contributes to the retention of inorganic and organic materials that may lead to acidosis and other manifestations of the disease. The distortion between the glomerular and tubular functions, moreover, may be important in determining the particular type of water and electrolyte abnormalities present in chronic renal failure. Thus, glomerular damage out of proportion to the impairment of tubular function predisposes to the retention of water and electrolytes. This might be the situation in acute episodes either in the initial attack or in the exacerbation. The opposite combination, however, could contribute to the demineralization or loss of electrolytes and fluid sometimes seen in the later course of the disease. Although changes of Tm_{PAH} or $Tm_{glucose}$ do not reflect directly what happens to electrolyte excretion, a reversal in the filtration rate to Tm ratio quite frequently occurs in patients with chronic nephritis just about the time the nephrotic syndrome disappears. This transition heralds the onset of the terminal phase of the disease, which may be characterized by water and salt depletion. Furthermore, it might be calculated that a small percentage of nephrons continuously diuretic because of impairment in electrolyte absorption could result in urine of low specific gravity. Impaired ability to concentrate, therefore, is not necessarily a measurement of any specific renal function. This mechanism could also, perhaps, explain the long persistence of impaired concentrating power frequently noted after acute diffuse glomerulonephritis has healed.

The fact that marked reduction of filtration rate should lead to retention of most substances filtered emphasizes the importance of the concept of alterations in renal tubular function. Such factors are undoubtedly important in arriving at the explanation of the rather varied changes observed in electrolytes in the terminal stages of nephritis. Although marked impairment of renal function ordinarily leads one to suspect that a patient may be threatened with hyperkalemia, hypokalemia is, in fact, more common in the terminal phases of chronic renal disease. Despite marked impairment of glomerular filtration rate, excessive amounts of potassium may be lost in the urine. Salt-losing nephritis is not common but, again, probably could be explained by a glomerular-tubular im-

balance. Inability of the kidneys to excrete hydrogen ion and to form ammonia, however, can also play a role in the situations characterized by loss of base. Compensatory hypertrophy of the parathyroids may lead to hypocalcemia. Tetany may or may not be evident, depending upon the degree of associated acidosis and other electrolyte abnormalities. Finally, anorexia and especially vomiting can further complicate the fluid and electrolyte pattern.

The course of events in the terminal phases of chronic glomerulonephritis is extremely variable and depends upon the combination of electrolyte changes due to renal functional impairment, the development of hypertension, the presence or absence of congestive heart failure and the degree of anemia. Another important consideration is the presence or absence of various other complications. Infections, anorexia, nausea and vomiting can lead to very serious consequences. Alternating lethargy and agitation or mental confusion, convulsions, uremic colitis and pericarditis are ominous manifestations.

F. HYPERTENSION IN GLOMERULONEPHRITIS

Hypertension may occur in several different phases of glomerulonephritis. It is quite common during the acute attack and even may occur before proteinuria and hematuria are evident. Generally, but not always, hypertension disappears about the same time the edema recedes. The exact mechanism of the production of hypertension in the acute phase of glomerulonephritis is not known. Perhaps it is renal in origin and due to the production or lack of inactivation of some humoral agent. Several workers (39) have demonstrated the presence of renin in the renal vein of patients with acute glomerulonephritis. Another probable factor is congestion of the circulation, which sometimes may be relieved by phlebotomy. Transient hypertension of similar characteristics may also occur in the exacerbation of chronic glomerulonephritis. Hypertension, however, is relatively uncommon in the latent phase of chronic glomerulonephritis. Even patients in the subacute accelerated phase of renal deterioration may be normotensive for several months. The presence or absence of hypertension is not strictly related to the amount of residual functioning renal mass in early or moderately advanced chronic glomerulonephritis. The incidence

XUM

of hypertension, however, increases as renal function falls below 30 per cent of normal (26).

G. TREATMENT

The treatment of glomerulonephritis for the most part consists of management of individual manifestations and symptoms as they arise. These will be discussed more or less in the order of their appearance.

1. Group A Hemolytic Streptococcus Infections

In view of the close association between acute glomerulonephritis and hemolytic streptococcus infections, prophylactic regimens of sulfonamides or penicillin should be as effective as they have proved to be in preventing acute rheumatic fever. Since the incidence of overt acute glomerulonephritis is relatively low and since the healing rate is high, a general prophylactic program directed toward this disease seems impractical. However, if an outbreak of streptococcus infections is shown to be due to a nephritogenic strain, or if a case of acute glomerulonephritis occurs in an institution such as a school, camp or asylum, or in a family group, prophylactic administration to exposed individuals of 100,000–200,000 units of penicillin orally three times daily for several weeks would appear to be a rational measure. If preferred, repository penicillin can be used (600,000 units benzathine penicillin intramuscularly, repeated 12–14 days later). Once manifestations of acute glomerulonephritis have developed, penicillin therapy is unlikely to affect the course of the disease or its prognosis. Nevertheless, penicillin treatment directed toward the infection is entirely reasonable. Such therapy should be of value not only in preventing complications, since the patient still may have active infection, but also in eradicating a nephritogenic organism which is a potential hazard to others. Further, despite suggestive evidence to the contrary, the possibility remains that prolonged existence of the streptococcus in the patient's tissue may contribute to the development of chronic glomerulonephritis. Unlike rheumatic fever, there appears to be no cogent reason for placing patients with chronic glomerulone-

phritis on prolonged prophylactic penicillin or sulfonamide therapy. Exacerbations in chronic glomerulonephritis are relatively uncommon as compared to the high incidence of repeated attacks of rheumatic fever. Furthermore, exacerbations in chronic nephritis do not appear to increase the rate of progression of the disease in the majority of patients.

2. Acute Glomerulonephritis

The patient with acute glomerulonephritis should be confined to bed.

Nutrition.—Dietary, fluid and electrolyte intakes require careful control. Protein and other foods of high potassium content such as citrus fruits should be omitted until a day or so after the onset of diuresis, at the time when excess retention of potassium is no longer a hazard. Another reason for limiting protein intake is based on experimental studies on anti-kidney serum nephritis in rats. These studies (40) indicate that a high protein intake increases the incidence and severity of the renal lesion and produces a high mortality. Conversely, a low protein diet administered to other rats given the same anti-kidney serum resulted in a lower incidence of disease which, when present, was relatively mild. Although there is no particular reason to suggest that these results can be translated to man, the conservative approach based on currently available knowledge is to restrict protein intake severely during the acute phase of glomerulonephritis. If anuria or significant oliguria is present, or if the patient has anorexia, nausea or vomiting, between 300 and 400 Gm. of carbohydrate should be administered daily to maintain nutrition and to prevent excessive metabolism of the patient's own tissues with the release of potassium. Such carbohydrate is administered intravenously as a 20–50 per cent solution. To avoid blood volume expansion, the daily infusion should take 24 hours. An indwelling polyethylene catheter in a large vein (preferably the femoral) is convenient for this purpose, but it should not be allowed to remain in a given vein for more than four days because of the danger of local thrombosis.

Perhaps the most important dietary consideration is the restric-

tion of sodium intake. The author believes that sodium intake should be limited to no more than 200 mg. per day, even in mildly ill patients. There seems to be little doubt that sodium intake can adversely affect the level of the blood pressure and also will lead to greater retention of body fluids. Fluids also should be sharply limited during the oliguric phase of acute nephritis, since continued intake in the presence of inability to excrete fluid will lead to congestion of the circulation with pulmonary edema, and may increase blood pressure and precipitate convulsions. Fluid intake during anuria or significant oliguria should be limited to no more than 300–700 ml. daily, depending on the age of the patient. If vomiting has been severe, however, the physician should be alert to the possibility of dehydration. The hematocrit is a valuable guide in this problem.

CIRCULATORY CONGESTION.—Digitalis is of little value in the treatment of circulatory congestion in nephritis except in the rare patient who also has organic heart disease and true congestive heart failure. But even this patient, if renal function is greatly impaired, can be but little if any benefited by digitalis since he has no way to excrete the excess fluid and salt. Phlebotomy of 400–600 ml. (proportionately smaller amounts in children) appears to be one of the most useful measures in this situation. Evaluation of the possible beneficial effects of phlebotomy may be obtained through a preliminary trial of "bloodless" phlebotomy. Blood pressure cuffs around three extremities are inflated to 15–25 mm. Hg below diastolic pressure. Careful observation is then made of blood pressure and symptoms. At present, diuretics are seldom used in the treatment of the edema of acute glomerulonephritis.

HYPERTENSION AND CONVULSIONS.—Magnesium sulfate may be very useful in controlling excessive hypertension and in treating convulsions. Thirty to 60 ml. of 50 per cent magnesium sulfate by mouth or rectum may be given every four hours to patients who have severe headache and vomiting. However, once convulsions or coma develops, magnesium sulfate should be given by injection. To children, 0.2–0.4 Gm./kg. body weight is given by intramuscular injection of a 25 per cent solution every four hours. The intravenous route, however, is to be preferred if at all feasible; 250 ml.

of a 2 per cent solution is given very slowly. This may be repeated in 12 hours if nitrogen retention is not present or is minimal. The dose should not be repeated if the patient has significant nitrogen retention since the plasma magnesium level will remain at high levels for days when renal function is impaired. During magnesium sulfate therapy the blood pressure must be followed closely to avoid excessive decreases. The intravenous injection of a barbiturate such as sodium Amytal frequently is a useful emergency measure in managing these patients.

Although some of the antihypertensive drugs, such as Ansolysen, appear to have a logical place in the management of hypertensive crises in acute nephritis, such therapy must be used with great caution in the presence of significant renal damage. If the patient is ill enough to require therapy of this type, the intravenous route probably should be used. Frequent and careful medical control is mandatory if such drugs are used in acute glomerulonephritis, since they almost uniformly reduce urine output and may depress other renal functions, especially if blood pressure is too rapidly reduced.

ELECTROLYTES.—Although common, most serum electrolyte abnormalities in acute glomerulonephritis require no therapy. Hyperchloremia is very common but seems quite innocuous. Serum sodium level is also frequently decreased. The physician, however, should resist his natural inclination to treat this laboratory finding by the administration of sodium. The decreased concentration of sodium in the serum in these circumstances is the result of retention of water in excess of sodium or, more likely, of an internal redistribution of sodium. The important point to remember is that the patient with edema, no matter what the serum sodium level is, has a greater than normal amount of the ion in his system.

Hyperkalemia is a serious threat when oliguria is severe and, when present, it requires the most vigorous therapy. Insulin and glucose can be given intravenously to control hyperkalemia promptly. Ordinarily, glucose is given as a 5 per cent solution. Twenty units of insulin is added for each 50 Gm. of glucose. Although the effects of this therapy are transient, they may be life-saving until excess potassium can be removed from the organism.

Repeated administration of a cation exchange resin designed to remove potassium is perhaps the most readily available simple technique for achieving this purpose, even in areas where an artificial kidney is available. Daily oral doses of 50 Gm. (20 Gm. in children) of the ammonium carboxylic resin are adequate. The resin should be suspended in glucose in water and given in small doses every two hours. The oral route is sometimes not feasible because of the frequent gastrointestinal upsets associated with renal failure. Retention enemas (10 per cent suspension of the resin in water) may be used, although this route yields much less uniform results. After two to three hours the resin is removed. Retention enemas of the resin may be repeated until the plasma potassium level is brought into a safe range. Oral resin therapy can be instituted as a prophylactic measure. If hyperkalemia is already present, it is important to realize that the exchange resins require 12–24 hours before serious hyperkalemia is controlled. Meanwhile emergency measures, such as glucose and insulin, should be instituted. Although calcium does not affect the plasma potassium level, it can control the cardiotoxic action of excess potassium. Such control, however, will persist only while calcium is being administered. A continuous intravenous infusion of calcium gluconate in glucose solution is the method of choice. Using a direct writing ECG machine as check, enough calcium is administered to eradicate the signs of hyperkalemia from the ECG. The rate of infusion is then adjusted so as to maintain the ECG as nearly as is possible. To avoid excess administration of fluid, the concentration of calcium in the infusion may need readjustment from time to time. Since the cardiotoxic effects of the hyperkalemia will reappear rapidly if the calcium infusion stops, the use of an indwelling polyethylene infusion catheter is wise.

Hyperkalemia can be controlled by the artificial kidney, but this apparatus is available in only a few clinics, and even in these is not often used routinely in the management of acute renal failure. Indeed, if medical management has been applied intelligently, the artificial kidney rarely will be necessary.

The anemia of acute glomerulonephritis requires no therapy since it is rarely severe and is partly the result of hemodilution.

BED REST.—One of the most important and difficult decisions to

make in the management of the patient with acute glomerulonephritis is when to allow the patient out of bed. As long as hypertension, edema and other signs and symptoms of acute nephritis persist, the patient should be kept in bed at as strict rest as is possible. Bed rest should be continued as long as the patient seems to be improving and, at the very least, until several days after the hypertension and all evidence of edema have disappeared. The erythrocyte sedimentation rate, which is increased in most patients with acute nephritis, can be used as a possible reflection of the activity of the disease. If, as often is the case, the patient still has proteinuria after all other signs (excluding hematuria and impaired concentrating ability) have disappeared, the attending physician has a difficult decision to make. He does not want to do anything that will jeopardize the eventual healing of the renal disease. On the other hand, there comes a time when continued bed rest becomes impractical or impossible, even though proteinuria may still be decreasing. If, for one reason or another, it is necessary to allow the patient out of bed before proteinuria disappears, the effect of ambulation on proteinuria, hematuria, blood pressure and renal function should be carefully studied. If proteinuria (24 hour excretion, not concentration) should increase markedly or if any other adverse finding should develop, the patient should return to bed for another week or so.

3. Exacerbation

The treatment of the exacerbation in chronic glomerulonephritis is the same as the initial acute attack, with the exception that it is not necessary to be as conservative in the matter of bed rest since the patient's underlying chronic disease will not heal. Thus, as soon as the acute manifestations are over, the patient may be allowed to be up and return to normal activity.

4. Latent Chronic Glomerulonephritis

No therapy is necessary for the patient in the latent phase of chronic glomerulonephritis. Diet and activity need not be modified.

Indeed, even in advanced chronic glomerulonephritis, active therapy or modification of diet or of daily activities is unnecessary until symptoms develop. However, very worth while is periodic study of the patient for the earliest evidence of the nephrotic phase, hypertension, electrolyte abnormalities, anemia or rapidly progressive functional impairment. Many nephritic manifestations are easier to treat when incipient than after being allowed to become full-blown.

5. Nephrotic Phase

One of the most difficult aspects of glomerulonephritis is treatment of the nephrotic syndrome. The logical management is replacement of the lost protein by intravenous administration of salt-poor, concentrated human serum albumin. However, such therapy can be of only transient benefit so long as the patient is excreting large amounts of protein in the urine. Such large amounts of serum albumin may be required to obtain effective results that its cost is prohibitive in the face of its temporary value. Substitutes for serum albumin such as gelatin and Dextran have a similar disadvantage. High protein diets are also disappointing. Acacia has been one of the most effective agents for the treatment of the nephrotic syndrome. Its use, however, has fallen into disrepute because of reported hepatic toxicity.

A trial of ACTH or cortisone therapy is probably warranted in most patients with the nephrotic syndrome. Sometimes these agents are quite effective, but the frequency of success is not great when the nephrotic syndrome is a manifestation of chronic glomerulonephritis in the adult. Either ACTH (75–100 mg. daily to adults, 50 mg. daily to children) or cortisone (300 mg. daily to adults, 200 mg. daily to children) may be used. The usual course is 10 days. If the first course is unsuccessful, second and third attempts are sometimes successful. Recently, previously resistant cases have responded to a combination of a course of ACTH or cortisone therapy and the administration of sufficient concentrated human salt-poor serum albumin to return the patient's serum albumin level to or near normal. The serum albumin administration generally is begun after seven to 10 days of hormone therapy. During the in-

tensive hormone therapy, sodium intake should be limited and extra potassium administered to avoid hypokalemic alkalosis. Once the nephrotic syndrome has responded, some workers now recommend that hormone therapy be continued for many months. This "maintenance" therapy is given on three consecutive days each week. When hormonal therapy fails, management is directed toward rigorous salt restriction combined with diuretics. Although the effects of the latter are frequently disappointing, the author does not hesitate to use mercurial diuretics until it becomes clear, after three or four trials, that they are completely ineffective. If ammonium chloride is used in an attempt to potentiate the effect of mercurial diuretics, great care must be observed if more than moderate renal functional impairment is present since such patients can easily be thrown into acidosis. Other diuretics such as aminophylline and the like may be tried, but generally are quite disappointing. Some success has been reported in the use of nitrogen mustard, but the results do not appear to be impressive.

6. Terminal Glomerulonephritis

Anemia of advanced chronic glomerulonephritis may become severe and be one of the most important contributors to the patient's weakness, dyspnea and other symptoms. Hence, anemia warrants careful study and treatment. Replacement of red blood cells is often of considerable benefit, but repeated transfusions are required since the bone marrow of these patients appears to be unable to form sufficient new cells. However, patients can be kept in relative comfort and able to work by judicious use of transfusions. Needless to say, great care must be observed when transfusions are given to patients with chronic glomerulonephritis who exhibit uremia, hypertension and perhaps some degree of congestive heart failure. Under these conditions, washed red blood cells are preferable to whole blood. They should be administered very slowly, with frequent checks on the venous pressure and of the lung bases for râles. Recently, oral administration of cobalt chloride (50–100 mg. daily at meal times, given in 20 mg. enteric-coated tablets) has been recommended for the anemia of chronic uremia. This therapy may take several months to achieve the desired effect

but, if effective, may be continued indefinitely and may perhaps obviate the necessity of blood transfusions. Gastrointestinal side-effects, however, frequently preclude the use of this agent.

CONGESTIVE HEART FAILURE.—This may be treated with digitalis and the other routine procedures. The response of congestive heart failure in chronic renal disease, however, is generally disappointing.

ELECTROLYTE ABNORMALITIES, some of which may be treated successfully, are very common in advanced chronic glomerulonephritis. Serum and urine electrolytes should therefore be measured in all cases. As discussed earlier, either hyper- or hypokalemia may develop in chronic nephritis. If *hypokalemia* requires replacement therapy, it should be given with caution and with frequent observations of the plasma potassium level and ECG. If potassium must be given intravenously, the concentration of potassium in the infusion fluid should not exceed 30 mEq./liter, and should be administered very slowly. Careful evaluation should be made each day to determine if further therapy is necessary, in order to avoid the hazards of overtreatment. Since retention of anions is common in advanced renal failure, the citrate or acetate salts rather than the chloride form of potassium may be used. *Hyperkalemia* may be treated as outlined for management of acute glomerulonephritis. Usually its treatment is unrewarding in chronic renal disease, but at least moderate restriction of protein (0.5 Gm./kg.) and of potassium-containing foods should be practiced when renal failure is severe.

RENAL DISTURBANCES.—Both decreased concentrating ability and vomiting may contribute to dehydration which may respond to salt administration. Inability of the kidneys to conserve base may lead to hyponatremia, which also may be corrected by salt administration if edema and congestive heart failure are not present. If hyponatremia is observed in the presence of the edema of the nephrotic syndrome or congestive heart failure, it is probably due to internal redistribution of sodium, and replacement therapy is rarely effective and often hazardous. Calcium loss, hypocalcemia and osteomalacia may also result from inability of the kidneys to conserve base. Tetany may not be evident despite hypocalcemia when acidosis is also present. In any case, calcium administration (10–15

ml. of 10 per cent calcium gluconate intravenously) may be beneficial.

Administration of alkaline salts such as ⅙M sodium lactate by infusion or sodium bicarbonate by mouth may be used to combat the acidosis of chronic renal failure. Such therapy must be used with careful control of urine pH, however, since damaged kidneys are unable to handle excess loads of alkali as well as acid. Furthermore, if hypocalcemia is present, the development of alkalosis may precipitate overt tetany. Finally, sodium administration carries the hazard of fluid retention.

Retention of anions as well as loss of base contributes to the acidosis of advanced chronic glomerulonephritis. An alkaline ash diet may slow the development of anion retention. Absorption of inorganic phosphates from the intestinal tract may be reduced by 30 ml. of aluminum hydroxide gel three times daily. The plasma inorganic phosphate level will be decreased. However, this may be undesirable since serum calcium also may be reduced and deposition of calcium in bones already deficient in calcium will be further impeded.

REFERENCES

1. Iverson, P., and Brun, C.: Aspiration biopsy of the kidney. Am. J. Med. 11:324, 1951.
2. Bjorneboe, M., *et al.*: The nephrotic syndrome: I. Histological changes illustrated by means of biopsy of the kidney. Acta. med. scandinav. 266 (supp.): 233, 1953.
3. Bright, R.: *Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy* (London: Longman, Rees, Orme, Brown & Greene, 1827).
4. Oliver, J. R.: *Architecture of the Kidney in Chronic Bright's Disease* (New York: Paul B. Hoeber, Inc., 1939).
5. Addis, T.: *Glomerular Nephritis: Diagnosis and Treatment* (New York: Macmillan Company, 1948).
6. Fishberg, A. M.: *Hypertension and Nephritis* (5th ed.; Philadelphia: Lea & Febiger, 1954).
7. Bell, E. T.: *Renal Diseases* (Philadelphia: Lea & Febiger, 1946).
8. Loeb, R. F.: Nephritis, in Cecil's *Textbook of Medicine* (9th; Philadelphia: W. B. Saunders Company, 1955), p. 1098.
9. Longcope, W. T.: Studies of the variations in the antistreptolysin titer of blood serum from patients with hemorrhagic nephritis: II. Observations on patients suffering from streptococcal infections, rheumatic

XUM

fever, and acute and chronic hemorrhagic nephritis, J. Clin. Invest. 15:277, 1936.

10. Lyttle, J. D., *et al.*: The serum antistreptolysin titer in acute glomerulonephritis, J. Clin. Invest. 17:631, 1938.
11. Rammelkamp, C. H., Jr., and Weaver, R. S. Acute glomerulonephritis: The significance of the variations in the incidence of the disease, J. Clin. Invest. 32:345, 1953.
12. Wertheim, A. R., *et al.*: The association of type specific hemolytic streptococci with acute glomerulonephritis, J. Clin. Invest. 32:359, 1953.
13. Updyke, E. L.; Moore, M. S., and Conroy, E.: Provisional new type of group A streptococci associated with nephritis, Science 121:171, 1955.
14. Rammelkamp, C. H., Jr., *et al.*: Epidemic nephritis, Tr. A. Am. Physicians 67:276, 1954.
15. Fischel, E. E., and Gajdusek, D. C.: Serum complement in acute glomerulonephritis and other renal diseases, Am. J. Med. 12:190, 1952.
16. Lange, K., *et al.*: Changes in serum complement during the course and treatment of glomerulonephritis, A.M.A. Arch. Int. Med. 88:433, 1951.
17. Smadel, J. E.: Experimental nephritis in rats induced by injection of antikidney serum: II. Preparation and immunological studies of nephrotoxin, J. Exper. Med. 64:921, 1936.
18. Schwab, L., *et al.*: Experimental hypersensitivity in the rabbit, J. Exper. Med. 91:505, 1950.
19. Seegal, D.: Acute glomerulonephritis following pneumococcic lobar pneumonia, Arch. Int. Med. 56:912, 1935.
20. Libman, E.: The clinical features of cases of subacute bacterial endocarditis that have spontaneously become bacteria-free, Am. J. M. Sc. 146:625, 1913.
21. Longcope, W. T.: The pathogenesis of glomerular nephritis, Bull. Johns Hopkins Hosp. 45:335, 1929.
22. Ellis, A.: Natural history of Bright's disease, Lancet 72:1, 34 and 72, 1942.
23. Seegal, D., and Earle, D. P., Jr.: A consideration of certain biological differences between glomerulonephritis and rheumatic fever, Am. J. M. Sc. 201:528, 1941.
24. Earle, D. P., Jr., *et al.*: The relation of the serum antistreptolysin titer to the exacerbation in chronic glomerulonephritis, J. Clin. Invest. 21: 491, 1942.
25. Rammelkamp, C. H., Jr.: Glomerulonephritis, Proc. Inst. Med. Chicago, 19:371, 1953.
26. Earle, D. P., Jr.; Taggart, I. V., and Shannon, J. A.: Glomerulonephritis: A survey of the functional organization of the kidney in

various stages of diffuse glomerulonephritis, J. Clin. Invest. 23:119, 1944.
27. Earle, D. P., Jr., *et al.*: Renal function and electrolyte metabolism in acute glomerulonephritis, J. Clin. Invest. 30:421, 1951.
28. Oliver, J.: When is the kidney not a kidney? J. Urol. 63:373, 1950.
29. Earle, D. P., Jr.: Renal function tests in the diagnosis of glomerular and tubular disease, Bull. New York Acad. Med. 26:47, 1950.
30. Peters, J. P.: Edema of acute nephritis, Am. J. Med. 14:448, 1953.
31. Davies, C. E.: Heart failure in acute nephritis, Quart. J. Med. 20: 163, 1951.
32. Farber, S. J., and Soberman, R.: J. Clin. Invest., in press.
33. Warren, J. V., and Stead, E. A., Jr.: The protein content of edema fluid in patients with acute glomerulonephritis, Am. J. M. Sc. 208: 618, 1944.
34. Loeb, E. N., *et al.*: On the permanence of recovery in acute glomerulonephritis, J. Clin. Invest. 17:623, 1938.
35. Seegal, D., *et al.*: On the exacerbation in chronic glomerulonephritis, J. Clin. Invest. 19:569, 1940.
36. Bloom, W. L., and Seegal, D.: The nephrotic phase: Its frequency of occurrence and its differential diagnostic value in determining the nature of the renal lesion in 120 patients who died of renal failure, Ann. Int. Med. 25:15, 1946.
37. Heller, B. I.; Jacobson, W. E., and Hammarsten, J. F.: The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosus, J. Lab. & Clin. Med. 37:133, 1951.
38. Barnett, H. L.; Forman, C. W., and Lawson, H. D.: The Nephrotic Syndrome in Children, in Levine, S. Z. (ed.) *Advances in Pediatrics* (Chicago: Year Book Publishers, Inc., 1952), Vol. V, p. 53.
39. Dexter, L.; Haynes, F. W., and Bridges, W. C.: Renal humoral pressor mechanisms in man: I. Preparation and assay of human renin, human hypertensinogen and hypertensin, J. Clin. Invest. 24:62, 1945.
40. Farr, L. E., and Smadel, J. E.: The effect of dietary protein on the course of nephrotoxic nephritis in rats, J. Exper. Med. 70:615, 1939.

XUM

XUM